REMARKS

The status of the application is as follows: claims 1-9 and 25-38 are pending and were rejected in a Final Office Action mailed December 1, 2006. Claims 10-24 were withdrawn from consideration pursuant to an earlier election. Applicant submits herewith a request for continuing examination under 37 C.F.R. §1.114, together with the required fee, and respectfully traverses the rejections.

Applicant and the undersigned thank the Examiner and his supervisor, Long Le, for the courtesies extended at the interview of May 11, 2007. The bases for objection to the Specification and the rejection of the claims were discussed generally as set forth below.

Objection to the Specification

1. In the Office Action, the Examiner repeated the objection to the Specification as indefinite regarding the recitation of "half life" of binding or "half life" of release. The Examiner relies on M.P.E.P 2161 as support for the proposition that the "requirements of 35 U.S.C. 112, first paragraph, are not merely limited to claimed subject matter, but are applicable to Applicant's entire specification. Thus, Examiner posits that the aforementioned objection to the specification is maintainable insofar as Applicant's entire specification does not enable one skilled in the art to make a capture device having a specific "half-life of binding" or a specific "half-life of release".

Applicant respectfully disagrees with the Examiner's interpretation of the requirements of 35 U.S.C. §112, first paragraph, which provides in pertinent part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same,..." (emphasis added)

The statute requires the applicant to enable those skilled in the art to make and use "the invention". The underlined terms, "it" and "the same", refer back to "the invention." M.P.E.P.

2164 provides in the opening paragraph that "[t]he enablement requirement refers to the requirement of 35 U.S.C. 112, first paragraph that the specification describe how to make and use the invention. The invention that one skilled in the art must be enabled to make and use is that defined by the claims(s) of the particular application or patent." (emphasis added).

M.P.E.P. 2161, which the Examiner cited, recites the first paragraph of §112 and then lists the three requirements, all in terms describing, enabling and disclosing the best mode of "the invention".

Without prejudice to Applicant's position that "half-life of binding" or "half-life of release" in the context of the Applicant's biomolecule capture device would be understood by those skilled in the art, Applicant invites the Examiner to note that none of the pending claims include the terms "half-life of binding" or "half-life of release". Thus, based on the clear terms of the statute and the M.P.E.P., there is no basis for the Examiner's objection.

2. In the Office Action, the Examiner also objected to the Specification as failing to provide proper antecedent basis for the claimed subject matter. The Examiner could not locate original support in the specification for the subject matter encompassed by the language "substrate comprising a polymer." Original basis can be found in the paragraph bridging pages 4, lines 27-30 to page 5, lines 1-3, wherein the specification states "[t]he present invention includes the use of a substrate, including ...and/or polymers including but not limited to a hydrogel, and/or polymer hydrogel array, each containing one or more reactive sites for the attachment of a biomolecule-binding compound... reactive sites can include ... exposed amino groups ...". *See also* page 5, lines 4-12, lines 17-20 and lines 22-24. *See also* page 8, lines 13-15 and lines 20-21.

Based on the foregoing, withdrawal of the objections to the Specification is respectfully requested.

Claim Rejections

1. 35 U.S.C. §102(b)

In the Office Action, the Examiner rejected claims 1-3, 5-9, 25 and 27-38 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 3,679,653 to Schuck & Wildi (the '653 Patent). The Examiner cited specifically col. 6, lines 19-28. Applicant respectfully disagrees with the Examiner's interpretation of the teachings of the '653 Patent and in support, submits herewith a schematic illustration of the differences between the polymer-hormone product of the '653 patent and Applicant's claimed biomolecule capture device.

In his rejection, the Examiner stated that the '653 patent "describes a biomolecule capture device ... comprising: ...

(b) a maleic anhydride compound (see col. 6, lines 19-28)

covalently bound to the surface of the substrate through a functional group at one of a 2 or 3 position of the maleic anhydride (see col. 5, lines 30 to col. 6, lines 12, "Z is a bivalent radical", "q is zero");

having an exposed carbonyl (see col. 5, line 30) for reversible covalent binding to a biomolecule ..."

With respect to part (b) above, Applicant submits that the manner in which the '653 patent employs maleic anhydride, and therefore, the function of the maleic anhydride, is different in significant respects than in Applicant's device. At col. 6, lines 15-28, the '653 patent states that a preferred polymeric material is the polymer of an olefinically unsaturated polycarboxylic acid or derivative with itself or in approximately equimolar portions with at least one other monomer copolymerizable therewith. The carboxylic acid derivative can be of the non-vicinal type or the vicinal type. Included within the vicinal type are maleic and α, α-dimethyl maleic acids and anhydrides of those acids. The '653 Patent thus teaches the use of maleic anhydride to make the polymeric substrate to which the hormone is then covalently bound. As shown in the attached schematics 1 and 2, whether the derivative is of the vicinal or the non-vicinal type, during the polymerization process, the maleic anhydride monomer necessarily loses its double

bond and becomes a succinic acid. The Examiner referenced the structure shown in col. 5, line 30 and noted that Z is a bivalent radical and q can be zero. When q is zero, there is a direct single bond between two adjacent carbon atoms. The carbon atom on the left in the structure drawn at line 30 is bound to four other atoms, one side of the bivalent Z, R_A, and two adjacent carbons. The carbon on the right in the structure drawn at line 30 is also bound to four other atoms, R_B, two adjacent carbons and another monomer in the polymeric chain.

In schematic 1 provided herewith, a synthesis of the ethylene: dimethyl maleic anhydride (EMA) copolymer described in col. 7 as preferred is shown as an example of a polymer having vicinal carboxylate groups. A synthesis of ethylene: acrylic acid copolymer is shown in schematic 2 as an example of a polymer having non-vicinal carboxylate groups. In both, it is apparent that the double bond in the maleic anhydride monomer starting material is necessarily changed to a single bond in order for the polymerization to take place. A polymerization terminates with the introduction of a terminator molecule or group, shown as Z^1 in schematic 1, to the reaction system. The terminator molecule or group Z, as shown, binds to end monomer in the chain at the free radical position. The terminator is not a maleic anhydride and would not function in the same way a maleic anhydride functions.

The loss of the double bond is significant because it renders the polymer-hormone bond essentially irreversible because it allows the free rotation around the C2-C3 single bond, as shown in schematics 3 and 4. The carboxyl group rotates away from the amide linkage so that reversal to the maleic anhydride form is not favored. The single bond therefore gives the polymer hormone product of the '653 patent increased stability, a quality found to be particularly advantageous for the '653 patent hormone-polymer products. As stated in the Summary of the Invention at col. 2 and again and again in the Examples in cols 10-11, the EMA-hormone product is much more stable than the native, or parent, hormone alone. The polymer-hormone product is intended for injection or ingestion by a patient in need of the hormone. It is intended to increase the life-span of the hormone in the face of continuous digestive action by serum proteases and other factors. See col. 1. In contrast, as shown in schematic 4, the double bond of the maleic anhydride is maintained in Applicant's biomolecule capture device. The double bond

[1] Note that Z as used in Schematic 1 is not intended to be the same as the bivalent radical, Z, in the '653 patent.

maintains a planar geometry, positioning the carboxyl group adjacent the biomolecule linkage so that reversibility upon a change in the pH is favored.

The Examiner appears to equate the statement in the '653 patent at col. 2, lines 15-17 that the "water-insoluble polymer-hormone product provide a low but continuous release of activity for implanted systems" with the reversibility of the covalent bond between biomolecules passed through Applicant's capture device and the maleic anhydride bound to the substrate of Applicant's device. Release of hormone activity is not the same as reversing a covalent bond at a selected pH. In fact, it is the exact opposite. The '653 patent attempts to avoid denaturation (and thereby inactivation) of the hormone caused by disruption of the interactive bonds which give the hormone its tertiary structure. It is the three dimensional, tertiary structure of the hormone that results in the desirable interactions of the native hormone. Digestion of the hormone breaks the bonds that yield the tertiary structure, thereby reducing or preventing the native activity of the hormone. The purpose of the polymer-hormone product of the '653 patent is to avoid denaturation and inactivation caused by breaking bonds. By binding the hormone to the polymer, the '653 patent increases the stability of the hormone and avoids loss of the tertiary structure that gives the hormone its activity. By continuous release of activity, the '653 patent means that the tertiary structure is maintained and therefore, the bonds within the hormone are not broken. That has nothing to do with reversing the bond between the polymer and the hormone. If that happened, the benefit of the polymer-hormone product would be lost.

Applicant submits that the '653 patent actually *teaches away* from a reversible bond between the hormone and its polymer substrate because to allow reversibility of that bond would eliminate the benefits of the product. Reversing the bond would destroy the hormone-polymer product's utility.

Schematic 4 provided herewith shows the difference in the structure of the Applicant's maleic anhydride-biomolecule reversible covalent bond and that of the '653 patent's hormone-polymer bond. In Applicant's device, the maleic anhydride maintains its double bond. It is not a unit of a polymer. It is attached to a polymer at the 2 or 3 position and links the biomolecule to the polymer under selected pH conditions. Upon alteration of the pH in the device, the covalent bond between the biomolecule and the maleic anhydride reverses. The biomolecules are then

free to be washed out of the device. Applicant's device provides a tool for separation of specific biomolecules, such as proteins, from a mixture of different types of biomolecules. It is not intended for *in vivo* use. Whereas the '653 patent's product would not work if the bond between the hormone and the polymer were to be reversed, Applicant's device would not work if the bond were not selectively reversible. The two systems use maleic anhydride for completely different purposes to provide completely different results. In one, the maleic anhydride monomer starting material is altered to make a polymer that will form a highly stable bond with a hormone. In the claimed capture device, the double bond of the maleic anhydride is not altered so that the bond between it and a biomolecule can be readily and completely reversed upon a selected change in pH.

Applicant submits that the '653 patent does not disclose each of the elements of the claimed biomolecule capture device of the Subject Application. Withdrawal of the rejection of claims 1-3, 5-9, 25 and 27-38 under 35 U.S.C. §102(b) is requested.

2. 35 U.S.C. §103(a)

The Examiner rejected claims 4 and 26 under 35 U.S.C. §103(a) as being unpatentable over the '653 patent in view of the Abstract of Schmincke-Ott & Bisswanger, 10 Prep. Biochem. 69 (1980). The Schmincke-Ott & Bisswanger Abstract describes a method of adsorbing proteins using aminohexylagarose. As Applicant stated in his prior response, it has nothing to do with a device comprised of a substrate having a maleic anhydride covalently bound to the substrate in an orientation that allows reversible capture of biomolecules. As described above, the '653 patent describes a polymeric substrate using maleic anhydride as one of the starting materials in the polymerization reaction. If aminohexylagarose were to be used as one of the monomers to make the polymer of the '653 patent, the resulting polymer would still not produce the claimed biomolecule capture device. The use of aminohexylagarose to capture proteins in the Schmincke-Ott & Bisswanger Abstract is via reversible, non-covalent, ionic interactions. If aminohexylagarose were used in place of the EMA polymer of the '653 patent, the polymer hormone bond would not form the stable covalent bond that is so necessary to the function of the '653 patent's hormone-polymer product. Thus, one skilled in the art would not be motivated to make that combination. It would not be obvious to combine references in a way that destroys the

function of the product of one of the references. According to M.P.E.P 2143.01, parts V and VI, the proposed modification can not render the prior art unsatisfactory for its intended purpose and can not change the principle of operation of the reference.

Applicant submits that the combination of the '653 Patent and the Schmincke-Ott & Bisswanger Abstract do not teach or suggest the subject matter of applicant's claimed biomolecule capture device and would not render the claimed device obvious to those of ordinary skill in the relevant art. Withdrawal of the rejection of claims 4 and 26 under 35 U.S.C. §103(a) is requested.

Supplemental Information Disclosure Statement

Applicant submits herewith a Supplemental Information Disclosure Statement with four references cited in a Search Report issued in the corresponding European patent application which was received less than three months ago and having claims similar to the original claims of the Subject Application. U.S. Patent No. 3,715,278, which was cited as general background, does not disclose a reversible reaction. The Magil et al. and Villain et al. articles describe tools for separation of peptides based on reactions with specific amino acids. Neither of these tools uses maleic anhydrides and neither appears to be of general use for a wide variety of biomolecules. WO 00/75164 is directed to a drug or gene therapy delivery system that speaks of the half life of the reactions (*see* page 33). The goal is the formation, for example, of DNA particles that are reversible under conditions found in a cell for delivery of the DNA or drug to a cell or tumor site and to allow passage of the drug or gene into a cell or specific cell organelles. The system uses maleic anhydride as one of many possible linkers to either block the membrane disruption capabilities of melitin and similar compounds defined therein as "membrane active compounds" which are known to disrupt cellular membranes, or to modify specific previously purified compounds for delivery to *in vivo* cells or tumor sites. Maleic anhydride is an example of one monomer that can be incorporated into the main chain (similar to the Schuck & Wildi polymerization) or into a side chain of a soluble polymer to link the polymer to an interaction modifier, or to link a membrane active compound to a compound that inhibits the membrane active compound. The pH characteristics of maleic anhydride are used to allow the bond between the maleic anhydride and the polymer to cleave (*see* page 54, lines 24-27) or to modify

specific purified compounds. WO 00/75164 does not describe a biomolecule capture device wherein the bond between a solid support polymer substrate and the maleic anhydride is maintained and the bond between the maleic anhydride and a biomolecule can be selectively reversed for separation of unmodified biomolecules from a complex mixture.

The references cited in the European Search Report do not disclose or render obvious the claimed biomolecule capture device of the Subject Application, but are disclosed herewith to satisfy Applicant's duty of disclosure and are discussed herein to advance the prosecution and allowance of the Subject Application.

Conclusion

Applicant again thanks the Examiner for his time and courtesy in meeting with Applicant and the undersigned. Reconsideration and allowance of all pending claims in light of the foregoing is earnestly solicited. If the undersigned can be of assistance in advancing the Subject Application to allowance or in addressing any issue the Examiner believes remains, the Examiner is urged to contact the undersigned at the number set forth below.

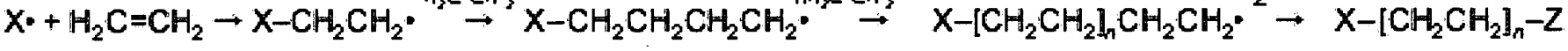
Respectfully submitted,

Christine R. Ethridge
Reg. No. 30,557

KIRKPATRICK & LOCKHART PRESTON GATES ELLIS LLP
Henry W. Oliver Building
535 Smithfield Street
Pittsburgh, PA 15222-2312
Phone: (412) 355-8619
Fax: (412) 355-6501

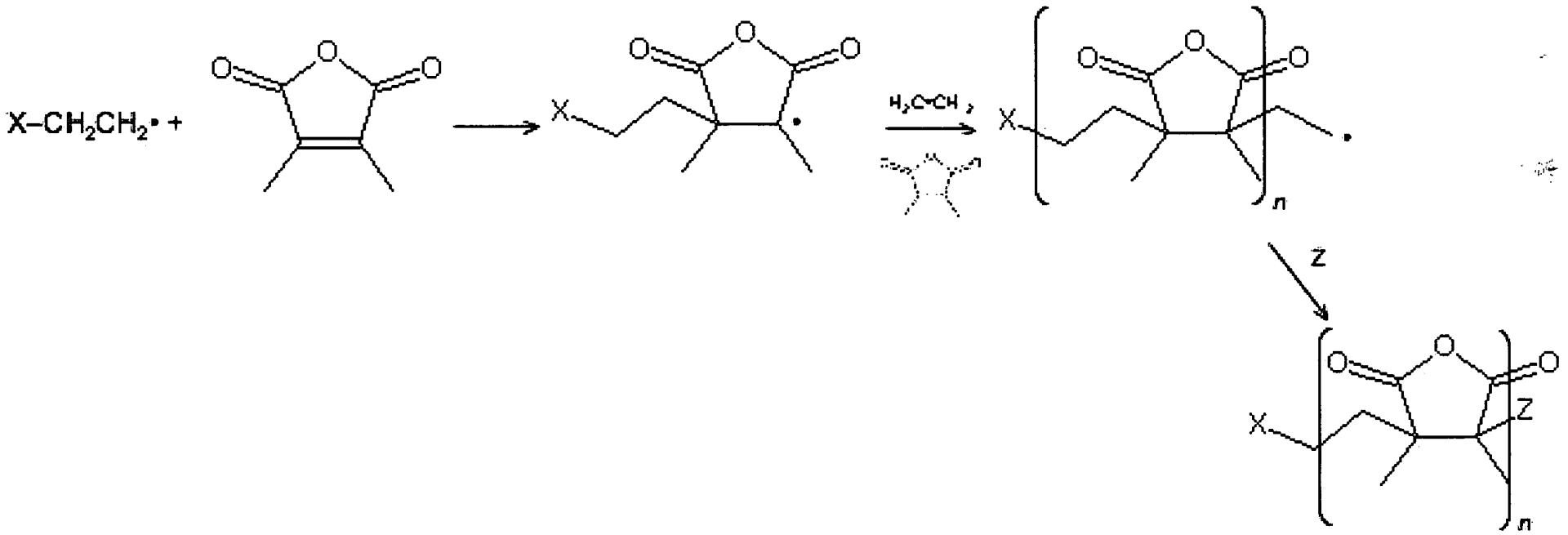
Schematic 1

Synthesis of polyethylene



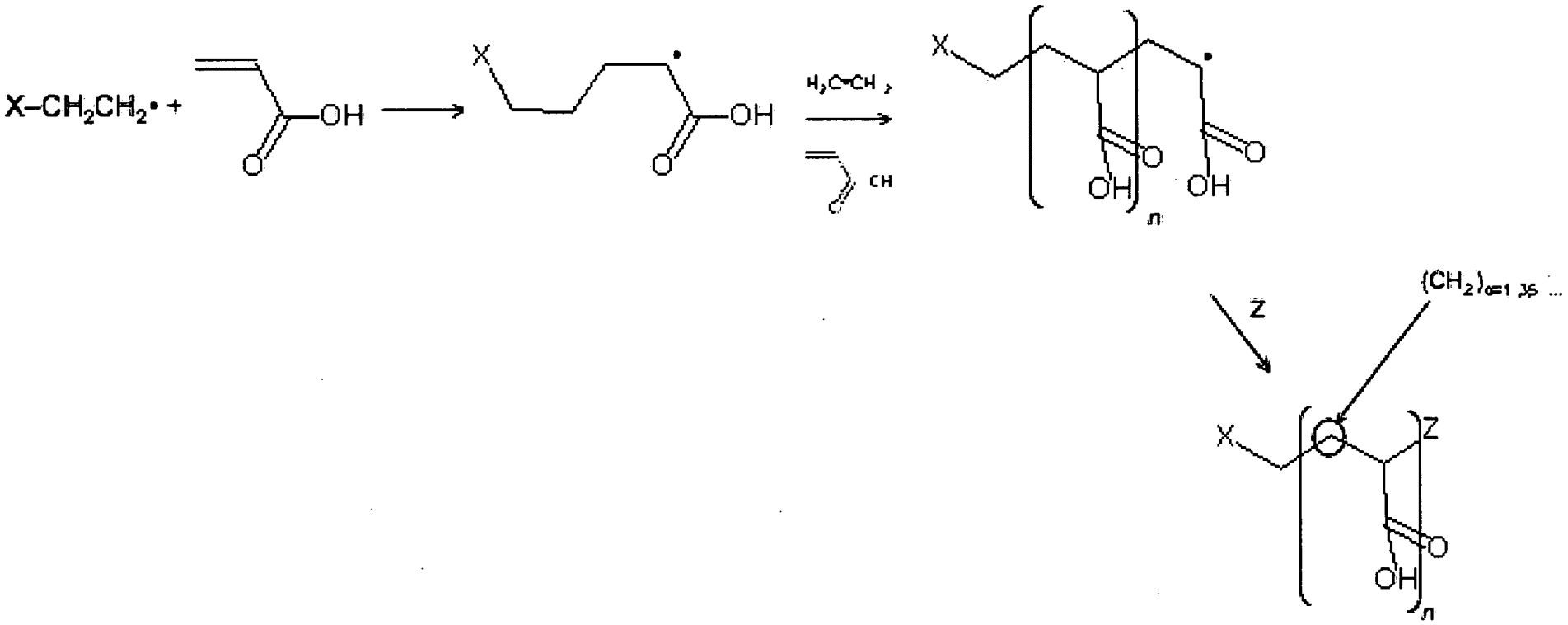
X• = initiator radial; Z = terminator

Synthesis of ethylene:dimethyl maleic anhdydride coploymer



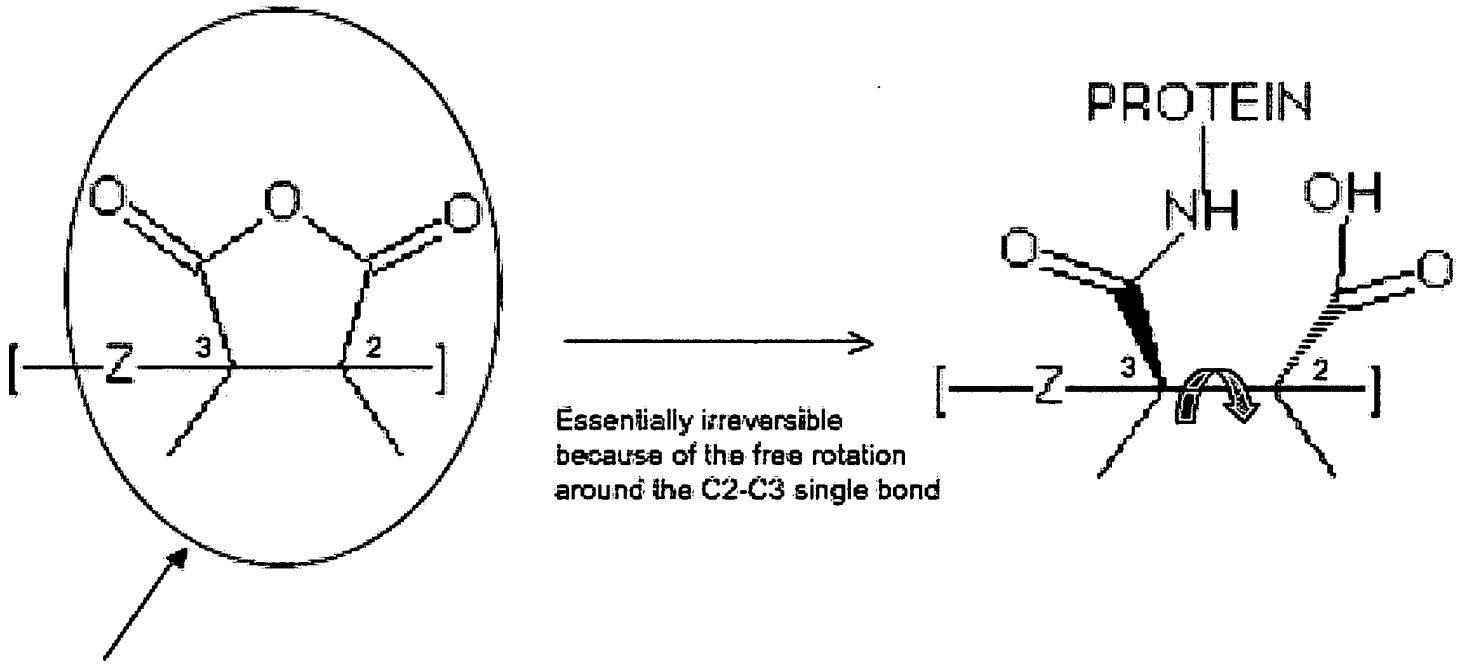
This makes polymers with vicinal (adjacent) carboxylate groups

Synthesis of ethylene:acrylic acid coploymer



This makes polymers with non-vicinal (non-adjacent) carboxylate groups. Note: This co-polymer randomly assorts ethylene and acrylic acid moieties. Schuck and Wildi were not quite accurate about the product of the non-vicinal reactions. Their *q* value in the non-vicinal case should be 1, 3, 5...

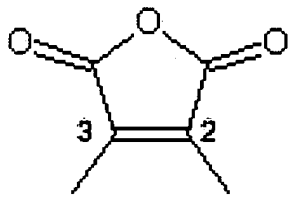
Schuck & Wildi polymer made from a dimethyl maleic anhydride co-polymer yields a polymer containing dimethyl succinic anhdyride



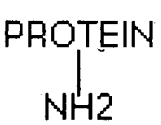
Dimethyl succinic anhydride co-polymer
(notice the lack of a C2-C3 double bond)

Schematic 4

Important differences between dimethyl maleic anhydride and dimethyl succinic anhydride

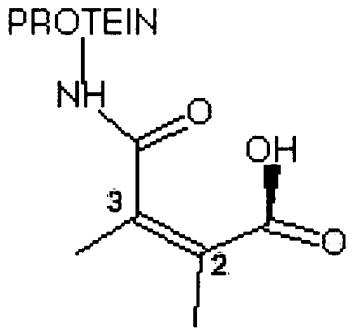


Dimethyl maleic anhydride

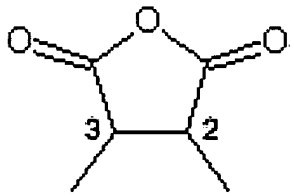


pH > 8

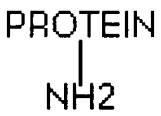
pH < 5



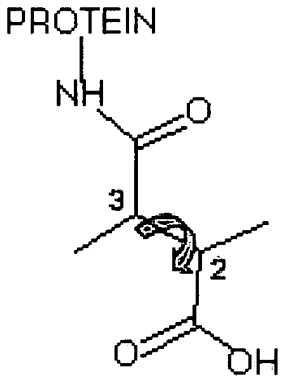
Highly reversible because the C2-C3 double bond Maintains a planar geometry that favors reversal at low pH



Dimethyl succinic anhydride



pH > 8



Essentially irreversible because of the free rotation around the C2-C3 single bond

Schuck & Wildi polymer with irreversible-linked protein is mostly insoluble, but "[t]he water-insoluble polymer-hormone products provide a low but continuous release of activity for implanted systems." This refers to solubility of the polymer-hormone, not the reversal of the covalent linkage between the polymer and the hormone.